The University of North Carolina and the American Chemistry Council Collaborated to Organize a Workshop

FORMALEHYDE SCIENCE INVITED EXPERTS WORKSHOP
UNDERSTANDING POTENTIAL HUMAN HEALTH CANCER RISK – FROM DATA INTEGRATION TO RISK EVALUATION
October 10 – 11, 2017
Location: UNC Friday Center, 100 Friday Center Drive, Chapel Hill, NC 27599

Co-Chairs: Drs. James Swenberg and Kenneth Mundt

Points for the discussions today:

- Background about formaldehyde
- The current risk assessment landscape
- The meeting itself – goal, invitees, session structure, topics
- Overview of some of the conclusions/recommendations from the meeting
- Recommendations for integrating data streams into a formaldehyde risk evaluation

Some Background about Formaldehyde

- At concentrations above 6 ppm in rats, where there is clear cytotoxicity and cell replication, it causes nasal cancer in rats.
- One of the most extensively studied chemical carcinogens
- Present in all cells at an appreciable level - tenths of mmoles/liter
- Estimated background exhaled concentrations of several ppb
- Endogenous formaldehyde-DNA reaction products have a high background
- Inconsistent epidemiology in occupational cohorts
- Risk assessments across the world are highly divergent

A View of the Risk Assessment Landscape

ORGANIZATION	POPULATION	APPROACH	RISK LEVEL	Basis of Decision
EU/ECHA	General	Qualitative but not low-dose linear	No convincing evidence of a carcinogenic effect at distant sites	Causes tumors above a threshold concentration by mechanisms that are initiated by the cytotoxic effects but …data does not allow firm conclusion on a threshold-mode of action"
Health Canada	General	Threshold Carcinogen DSL Low priority substance	**2.3×10^{-10} at 1 ppb**	Carcinogenic hazard to humans "…under conditions that induce cytotoxicity and sustained regenerative cell proliferation."
Occupational Standards from various bodies In the US and EU	Workers	Threshold Carcinogen	Exposure standards: TWAs with STELs 0.1 ppm ACGIH; 0.016 pp NIOSH; NIOSH; 3ppm MAK and SCOEL	Varied: from MAK - Cancer classification 4: non-genotoxic; cell proliferation important to MoA to ACGIH's "cancer classification A1: confirmed human carcinogen "
NTP Report on Carcinogens (2011)		Qualitative	Known human carcinogen	Sufficient evidence in humans for nasal tumors and myeloid leukemia
IARC Monographs 10F (2010)		Qualitative	Known human carcinogen	Sufficient evidence in humans for tumors at both sites
IRIS (2010)	General	Low dose linear	**1×10^{-4} at 1 ppb**	For NPC, mutagenic MoA operating in conjunction with key event of formaldehyde cytotoxicity-induced cell proliferation; sufficient evidence of causal association for NPC and LHP cancer in humans

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With ongoing work on a new IRIS assessment, it was considered an opportune time to bring together highly-regarded, subject matter experts and discuss how diverse data streams could be brought together to conduct an up-to-date risk evaluation

Formaldehyde Science Invited Experts Workshop Attendee List

Name	Affiliation	Email
Bruce Rodan	Environmental Protection Agency	Rodan.bruce@Epa.gov
Chap Thompson	ToxStrategies, Inc.	cthompson@toxstrategies.com
David Coggon	University of Southampton	dnc@mrc.soton.ac.uk
Enrico Pira	University of Turin	enrico.pira@unito.it
Erin Dickison	American Chemistry Council	Erin_Dickison@americanchemistry.com
Gary Marsh	University of Pittsburg	gmarsh@pitt.edu
Harvey Checkoway	University of California San Diego	hcheckoway@ucsd.edu
Harvey Clewell	ScitoVation/Ramboll Environ	hclewell@scitovation.com
Heinz-Peter Gelbke	Consultant to Formacare	heinz-peter.gelbke@gmx.de
Helmut Greim	Independent Consultant	helmut.greim@lrz.tu-muenchen.de
Hermann Bolt	Independent Consultant	h.m.bolt@me.com
Iris Camacho	Environmental Protection Agency	Camacho.Iris@epa.gov
Jim Bus	Exponent	jbus@exponent.com
Jim Sherman	Celanese	James.Sherman@celanese.com
Jim Swenberg	University of North Carolina	jswenber@email.unc.edu
Kenneth Mundt	Ramboll Environ	kmundt@ramboll.com
Kimberly White	American Chemistry Council	kimberly_white@americanchemistry.com
Kris Thayer	Environmental Protection Agency	thayer.kris@epa.gov
Mark Gruenwald	Hexion	mark.gruenwald@hexion.com
Mel Andersen	ScitoVation	mandersen@scitovation.com
Michael Thirman	University of Chicago	mthirman@medicine.bsd.uchicago.edu
Paolo Boffetta	Icahn School of Medicine at Mount Sinai	paolo.boffetta@mssm.edu
Raj Sharma	Georgia-Pacific	raj.sharma@gapac.com
Robinan Gentry	Ramboll Environ	rgentry@ramboll.com
Rory Conolly	Environmental Protection Agency	Conolly.rory@Epa.gov
Sam Cohen	University of Nebraska Medical Center	scohen@unmc.edu
Stewart Holm	American Forest & Paper Association	Stewart_Holm@afandpa.org
Sue MacMillan	Oregon Department of Environmental Quality	susan.macmillan@state.or.us
Tom Starr	TBS Associates	tbstarr@email.unc.edu

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TUESDAY, OCTOBER 10, 2017	
Time	**Item**
8:00am – 9:00am	**BREAKFAST** (UNC Friday Center – Main Vestibule and Dining Area)
8:00am – 9:00am	**REGISTRATION** (Outside of Conference Room: Tentatively Mountain Laurel)
9:00am -9:05am	**Welcome and Logistics** - Kimberly White and Jim Swenberg (5 minutes)
9:05am -9:10am	**Workshop Purpose and Objectives** - Ken Mundt (5 minutes)
9:10am -9:25am	**Understanding the Formaldehyde Science and Putting the Puzzle Pieces Together – Integrating New Science into Risk Evaluation Processes** - Robinan Gentry (15 minutes)
9:25am – 9:40am	**Summary of Global Risk Assessment Approaches for the Formaldehyde Science - General Approaches in EU, Canada, WHO and the US** - Jim Bus (15 minutes)
SESSION 1: INTEGRATING THE FORMALDEHYDE SCIENCE ON NASAL CARCINOGENICITY AND POTENTIAL FOR CAUSALITY (Chair: Helmet Greim)	
9:40am – 10:00am	**European Approach for Evaluating the Formaldehyde Science: OEL, Nasal Impacts and Threshold Assessment** - Hermann Bolt (20 minutes)
10:00am -10:20am	**Formaldehyde and Nasal Carcinogenicity: What Does the Epidemiology and Animal Data Tell Us?** - Gary Marsh (20 minutes)
10:20am – 12:00pm	**Discussion – Key Views by Participants on Charge Questions and MOA Framework** • Charge Question #1 Discussion (25 minutes) • Charge Question #2 Discussion (25 minutes) • Charge Question #3 Discussion(25 minutes) • Open Discussion (25 minutes)
12:00pm – 12:45pm	**LUNCH** (UNC Friday Center – Main Vestibule and Dining Area)
SESSION 2: INTEGRATING THE FORMALDEHYDE SCIENCE ON LHP CANCER AND POTENTIAL FOR CAUSALITY (Chair: Ken Mundt)	
12:45pm – 1:05pm	**Key Events and Considerations for LHP Cancers** - Ken Mundt (20 minutes)
1:05pm – 1:25pm	**Overview: Epidemiology Evidence** - Harvey Checkoway (20 minutes)
1:25pm – 1:45pm	**Overview of the Animal Science** - Chad Thompson (20 minutes)
1:45pm – 2:05pm	**LHP Cancers and Biological Plausibility – Can Exogenous Formaldehyde Reach the Bone Marrow?** Jim Swenberg (20 minutes)
2:05pm – 3:45pm	**Discussion - Key Views by Participants on Charge Questions and MOA Framework** • Charge Question #4 Discussion (25 minutes) • Charge Question #5 Discussion (25 minutes) • Charge Question #6 Discussion (25 minutes) • Open Discussion (25 minutes)
3:45pm – 4:00pm	**BREAK** (UNC Friday Center – Main Vestibule and Dining Area)
4:00pm – 4:15pm	**Looking Across Data Streams to Draw Conclusions Regarding Causality: Key Considerations in the Formaldehyde Science** Harvey Clewell (15 minutes)
4:15pm – 5:30pm	**Discussion – Key Views by Participants on Charge Questions** • Charge Question #7 Discussion (30 minutes) • Charge Question #8 Discussion (30 minutes) • Open Discussion (15 minutes)
5:30pm	**ADJOURN DAY 1 OF WORKHOP**
6:30pm – 8:00pm	**DINNER – OFFSITE** (Location: TBD)

WEDNESDAY, OCTOBER 11, 2017	
Time	**Item**
8:00am – 9:00am	**BREAKFAST** (UNC Friday Center – Main Vestibule and Dining Area)
8:00am – 9:00am	**REGISTRATION** (Outside of Conference Room: Tentatively Mountain Laurel)
SESSION 3- FORMALDEHYDE –DATA RICH CHEMICAL RIPE FOR RISK EVALUATION? (Chair: Jim Sherman)	
9:00am – 9:15am	**Overview of State-of-the-Science Approaches for Data Integration** - Kimberly White (15 minutes)
9:15– 9:30am	**Recap of Day 1 Discussion: Identified Data Gaps and Uncertainties - Information Needs for a Formaldehyde Risk Evaluation** Mel Andersen (15 minutes)
9:30am – 11:45am	**Discussion – Key Views by Participants on Charge Questions** • Charge Question #9 Discussion (20 minutes) • Charge Question #10 Discussion (30 minutes) • Charge Question #11 Discussion (30 minutes) • Charge Question #12 Discussion (20 minutes) • Charge Question #13 Discussion (20 minutes) • Open Discussion (15 minutes)
11:45am – 12:00pm	**Workshop Wrap and Next Steps**
12:00pm	**LUNCH** (UNC Friday Center – Main Vestibule and Dining Area)
1:00pm	**ADJOURN DAY 2 OF WORKSHOP**

SESSION 1: INTEGRATING THE FORMALDEHYDE SCIENCE ON NASAL CARCINOGENICITY AND POTENTIAL FOR CAUSALITY

1. Does the available scientific evidence support a specific MOA and causal association with NPC?
    - What mechanistic evidence is available to support the proposed modes of action frameworks discussed for NPC? What are the uncertainties?

   Suggested Discussants for Charge Question: Mel Andersen, Hermann Bolt , Harvey Clewell, Rory Conolly, Gary Marsh

2. What are the key animal data for characterizing the shape of the dose-response curve for formaldehyde-induced nasal tumors? What are the key epidemiological studies for formaldehyde-induced nasal tumors and how would you reconcile differences between those studies?
    - If a causal association can be established for human, what exposure metrics are associated with evidence of carcinogenicity? Is there evidence of a threshold for NPC in humans?

   Suggested Discussants for Charge Question: Mel Andersen, Herman Bolt, Harvey Clewell, , Rory Conolly, Peter Gelbke, Helmut Greim, Gary Marsh

3. What quantitative methods (e.g., linear and non – linear low dose extrapolation, threshold, PBPK modeling for dose-response assessment) would best characterize the potential for NPC risk in humans?
    - Are there uncertainties with any of these quantitative methods that suggest this type of modeling should not be applied?

   Suggested Discussants for Charge Question : Harvey Clewell, Rory Conolly, Robinan Gentry, Tom Starr

SESSION 2: INTEGRATING THE FORMALDEHYDE SCIENCE ON LHP CANCER AND POTENTIAL FOR CAUSALITY

4. What does the totality of the animal and epidemiology evidence tell us about the potential for a causal association with LHP and what conclusions can be drawn?
    - What role does endogenous production play in drawing conclusions regarding LHP?
    - Do the available data support a specific mode of action for hematopoietic cancers?

   Suggested Discussants for Charge Question: Paulo Bofetta, Harvey Checkoway, David Coggon, Sam Cohen, Robinan Gentry, Joseph Haney, Erico Pira, Jim Swenberg, Michael Thirman, Chad Thompson

5. What mechanistic data are critical to understanding a causal association between formaldehyde exposure and specific hematopoietic cancers?
   Suggested Discussants for Charge Question: Rory Conolly, Tom Starr, Jim Swenberg, Michael Thirman

6. Do epidemiology studies provide useful dose-response data for LHP?
   Suggested Discussants for Charge Question: Rory Conolly, Tom Starr, Jim Swenberg Michael Thirman

7. What methods for assessing causality and evidence integration are best applied to the available data for LHP cancer for conducting a hazard assessment (e.g., Bradford Hill criteria, biological systems approach, hypothesis based weight of evidence framework, systematic review, combination of approaches?)
   Suggested Discussants for Charge Question: Mel Andersen, Paulo Boffetta, Harvey Checkoway, David Coggon, Ken Mundt, , Enrico Pira, Kris Thayer

8. What uncertainties are important for consideration when integrating the available evidence? **Suggested Discussants for Charge Question:** Mel Anderson, Jim Bus, Harvey Clewell, Sam Cohen, Robinan Gentry, Tom Starr

SESSION 3- FORMALDEHYDE –DATA RICH CHEMICAL RIPE FOR RISK EVALUATION?

9. What should be considered as the problem formulation and questions to be addressed when conducting a formaldehyde risk evaluation?

10. What are the best available approaches to conduct a robust evaluation of formaldehyde carcinogenic potential?

11. How can the approaches used to evaluate and integrate scientific evidence inform the risk assessment?
    - What aspects of the Biological Systems Approach can be used to integrate the formaldehyde data?
    - How can hypothesis based weight of evidence approach be to integrate the data streams for determination of causality?

12. What needs to be added or changed in the draft IPCS Mode of Action Framework nasal carcinogenicity?

13. What is the comparative weight of evidence for each hypothesized mode of action for nasal carcinogenicity?

Suggested Discussants for All Charge Questions – All Participants

Today, we want to convey a sense of the discussions, conclusions and recommendations from the group for the path forward

I. Dr. Swenberg - formaldehyde DNA-reaction products in various tissues from rodents and monkeys and their implications for responses to formaldehyde beyond the front of the nose.

II. Dr. Mundt – key recent epidemiological evaluations related to NPC, AML and Mode of Action

III. Dr. Andersen – recommendation for integrating the rodent and human studies into a more quantitative risk evaluation for formaldehyde.

I. Dr. Swenberg - formaldehyde DNA-reaction products in various tissues from rodents and monkeys

Formaldehyde-Induced DNA-Protein Crosslinks

- DNA-Protein Crosslinks (DPCs) have long been known to be genotoxic.
- Heck and Casanova conducted extensive studies on rats and primates exposed to radiolabeled formaldehyde.
- We have now developed a chemical-specific method for the dG-OHMe-cysteine DPC that can measure both endogenous and exogenous DPC.

Time to Steady-State for Exogenous [$^{13}CD_2$]-HO-CH2-dG Adducts in Nasal Epithelium

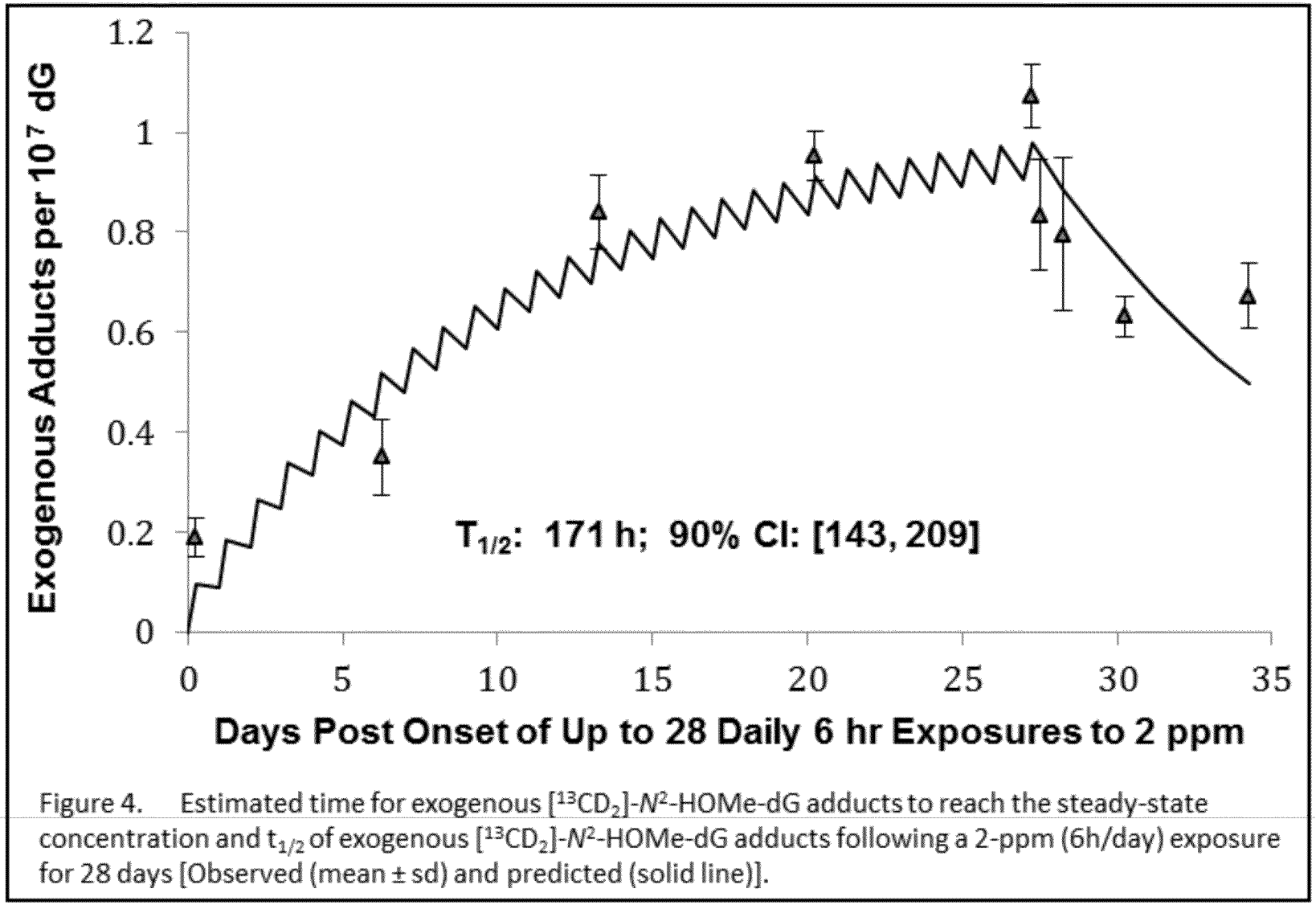
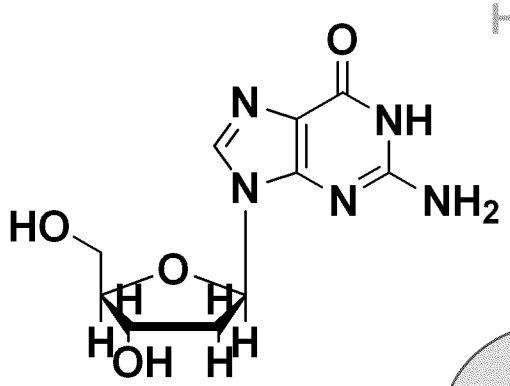
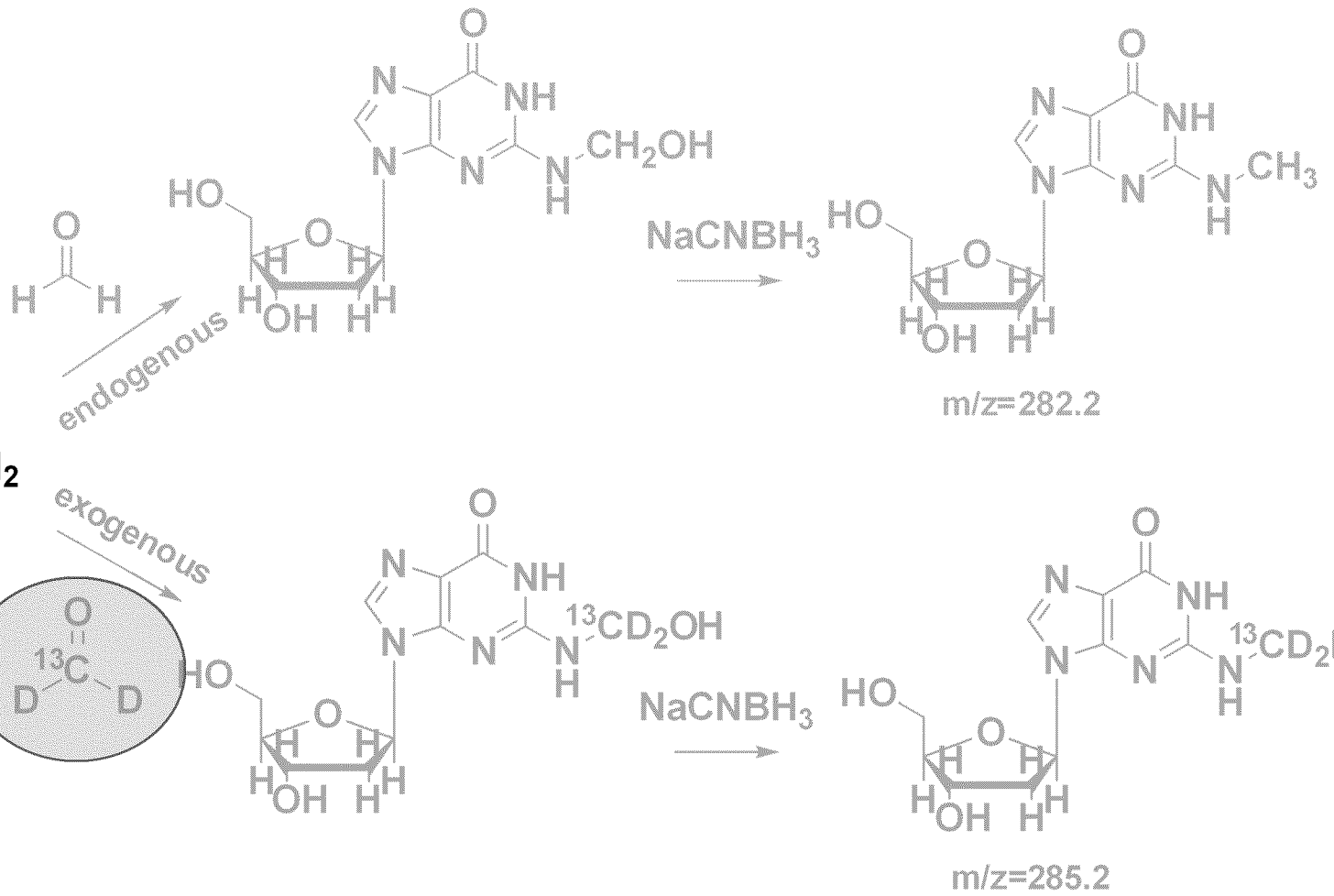


Figure 4. Estimated time for exogenous [$^{13}CD_2$]-*N*^{2}-HOMe-dG adducts to reach the steady-state concentration and $t_{1/2}$ of exogenous [$^{13}CD_2$]-*N*^{2}-HOMe-dG adducts following a 2-ppm (6h/day) exposure for 28 days [Observed (mean ± sd) and predicted (solid line)].

Looking at *Adducts* originating from both endogenous and exogenous formaldehyde.

- $^{13}CD_2O$ Exposure
- Tissue Collection
- DNA Isolation
- Reduction with $NaCNBH_3$
- Digestion and HPLC Fractionation
- Nano-LC-MS/MS



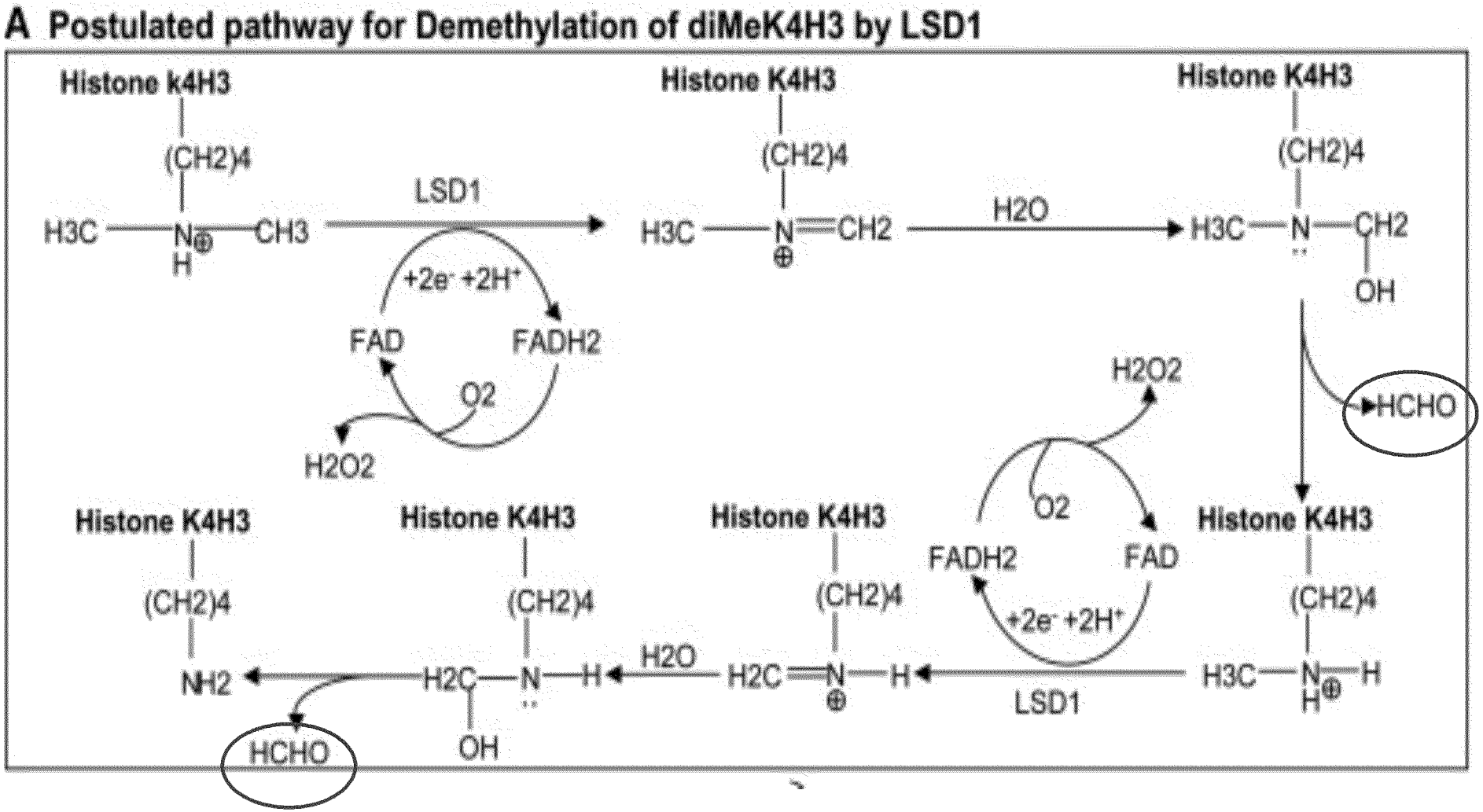


Formation of N^2-HOMe-dG mono-adducts (mean ± SD) in rat nasal epithelium, bone marrow and white blood cells exposed to 2-ppm labeled formaldehyde for 28 days.

Exposure period	Rat nasal epithelium N^2-HOMe-dG (adducts/10^7 dG)			Rat bone marrow N^2-HOMe-dG (adducts/10^7 dG)			Rat white blood cells N^2-HOMe-dG (adducts/10^7 dG)		
	Endogenous [a]	Exogenous	n	Endogenous [a]	Exogenous	n	Endogenous [a]	Exogenous	n
7 days	2.51 ± 0.63	0.35 ± 0.17	5	3.37 ± 1.56	n.d.	6	2.62 ± 1.12	n.d.	4
14 days	3.09 ± 0.98	0.84 ± 0.17	5	2.72 ± 1.36	n.d.	6	2.26 ± 0.46	n.d.	4
21 days	3.34 ± 1.06	0.95 ± 0.11	5	2.44 ± 0.96	n.d.	6	2.40 ± 0.47	n.d.	4
28 days	2.82 ± 0.76	1.05 ± 0.16	6	3.43 ± 2.20	0.34 [b]	12	2.49 ± 0.50	n.d.	4
28 days + 6h post expo	2.80 ± 0.58	0.83 ± 0.33	9	2.41 ± 1.14	n.d.	6	2.97 ± 0.58	n.d.	4
28 days + 24h post expo	2.98 ± 0.70	0.80 ± 0.46	9	4.67 ± 1.84	n.d.	5	2.57 ± 0.58	n.d.	4
28 days + 72h post expo	2.99 ± 0.63	0.63 ± 0.12	9	5.55 ± 0.76	n.d.	6	1.75 ± 0.26	n.d.	4
28 days + 168h post expo	2.78 ± 0.48	0.67 ± 0.20	10	2.78 ± 1.94	n.d.	4	2.61 ± 1.22	n.d.	4
Air control	2.84 ± 0.54	n.d.	8	3.58 ± 0.99	n.d.	6	2.76 ± 0.66	n.d.	6

[a] No statistically significant difference was found using the two-sided Dunnett's test (multiple comparisons with a control) (Dunnett, 1964). [b] The amount of exogenous N^2-HOMe-dG adducts that was found in only one bone marrow sample analyzed by AB SCIEX Triple Quad 6500. n.d. = not detected.

Some of the Endogenous Formaldehyde Arise from Demethylation of Histone 3 in the Nucleus



Shi *et al.* Cell, 2004 ; 119(7):941-953. (Cited over 1,100 times)

dG-Me-Cys in Rats Exposed to High Levels of Formaldehyde

Rats Exposed to 15 ppm

Formaldehyde induced dG-Me-Cys in nose, PBMC and bone marrow of rats exposed to **15 ppm of formaldehyde (6 h per day)**

Tissue	Exposure period (day)	dG-Me-Cys (crosslink/10^8 dG)	
		Endogenous	Exogenous
Nose	0	6.50 ± 0.30 (n=5)	ND*
	1	4.42 ± 1.10 (n=6)	5.52 ± 0.80
	2	4.28 ± 2.34 (n=6)	4.69 ± 1.76
	4	3.67 ± 0.80 (n=6)	18.18 ± 7.23
PBMC	0	4.98 ± 0.61 (n=5)	ND
	1	3.26 ± 0.73 (n=4)	ND
	2	3.00 ± 0.98 (n=5)	ND
	4	7.19 ± 1.73 (n=5)	ND
Bone Marrow	0	1.49 ± 0.43 (n=3)	ND
	1	1.67 ± 0.18 (n=3)	ND
	2	1.66 ± 0.57 (n=3)	ND
	4	1.41 ± 0.21 (n=3)	ND

* ND, Not detected

Similar responses are seen in Primates

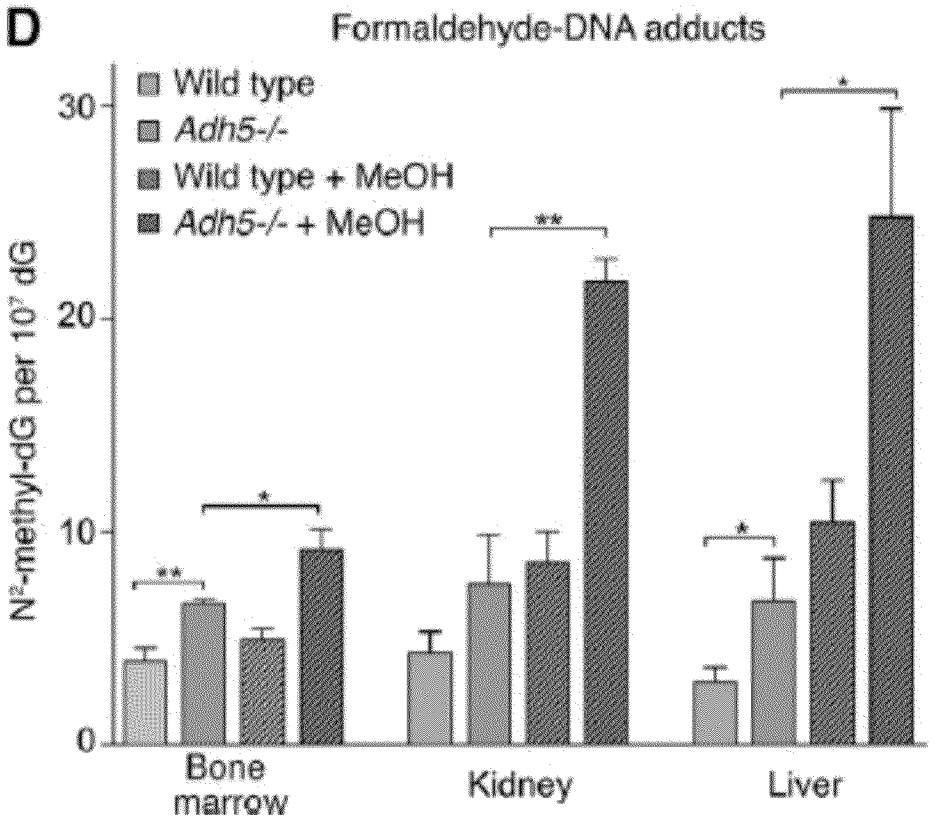
Formaldehyde induced dG-Me-Cys in nose, PBMC and bone marrow of primates exposed to 6 ppm of formaldehyde (6 h per day)

Tissue	Exposure period (day)	dG-Me-Cys (crosslink/10^8 dG)	
		Endogenous	**Exogenous**
Nose	0	3.59 ± 1.01 (n=5)	ND
	2	3.76 ± 1.50 (n=5)	1.36 ± 0.20
PBMC	0	1.34 ± 0.25 (n=5)	ND
	2	1.57 ± 0.58 (n=4)	ND
Bone Marrow	0	2.30 ± 0.30 (n=4)	ND
	2	1.40 ± 0.46 (n=5)	ND
Liver	0	15.46 ± 1.98 (n=6)	ND
	2	11.80 ± 2.21 (n=6)	ND

* ND, Not detected

Formaldehyde derived DNA reaction products in various tissues from formaldehyde precursors

- A variety of compounds are metabolized to formaldehyde – e.g., methanol, caffeine, aspartame, many drugs.
- Tissue formaldehyde adducts are found after with dosing mice methanol.
- With formaldehyde, no DNA-adducts are found at sites other than in the front of the nose in either rats or the non-human primates.
- **Inhaled formaldehyde does not reach these other tissues**



Pontel *et al*. Molecular Cell, 2015; 60(1):177-188

Ongoing Studies on Formaldehyde DNA-reaction products

- Low dose exposures in rats (air control, 1 ppb, 30 ppb, 300 ppb)
- Breath analysis shows approximately 1-2 ppb in humans
- 1 ppb is approximately the same as breath analysis with no exposure to formaldehyde
- Expected completion of mass spectrometry by January 2018

II. Key New Epidemiological Evidence/Analyses: NPC, AML and Mode of Action – Dr. Kenneth Mundt

- Marsh et al. (2014, 2016) challenge conclusion of NPC association as "neither consistent with the available data nor with other research findings"
  - "driven heavily by anomalous findings in one study plant (Plant 1)"
  - Nasal/sinus cancers seemed more plausible than NPC, but increased risk not seen.
- Checkoway et al. (2015) reanalysis of Beane Freeman et al. (2009)
  - Separated myeloid leukemias into acute (AMLs) and chronic (CML)
  - Associations seen with Hodgkin lymphoma and CML, but not observed in other studies
  - Evaluated associations with "peak" exposure
- Gentry et al. (2013) and Mundt et al. (2017) reanalysis of Zhang et al. (2010) demonstrate no association between formaldehyde exposure and any reported outcome among exposed workers.

No excess mortality from AML or CML observed

	Checkoway et al. 2015				Beane Freeman et al. 2009			
	Non-exposed (n=3,136)		Exposed (n=22,483)		Non-exposed (n=3,108)		Exposed (n=22,511)	
	Obs	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**	**Obs**	**SMR (95% CI)**
Myeloid leukemia	4	**0.69** (0.19-1.76)	44*	**0.86** (0.64-1.16)	4	**0.65** (0.35–1.74)	44	**0.90** (0.67–1.21)
AML	4	**0.93** (0.25-2.37)	30	**0.80** (0.56-1.14)	NR		NR	
CML	0		13	0.97 (0.56-1.67)	NR		NR	

US mortality rates used as the reference

*One death was coded to ICD-8 205.9, unspecified myeloid leukemia.

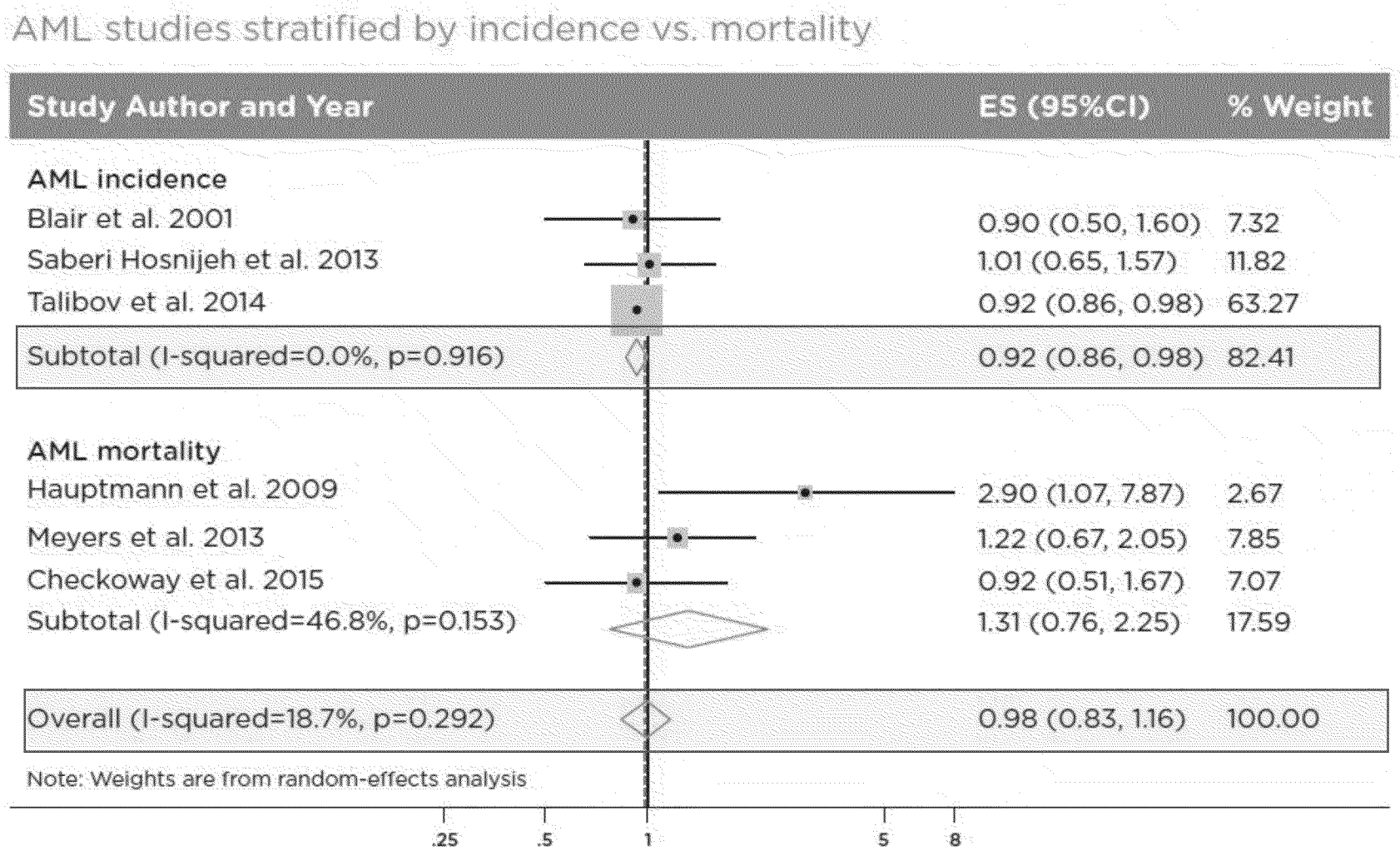
Association between peak exposure and mortality using most specific diagnosis (Checkoway et al. 2015)

	No peak		≥2.0 to < 4.0 ppm		≥4.0 ppm		
Diagnosis	**Obs**	**HR (95% CI)**	**Obs**	**HR (95% CI)**	**Obs**	**HR (95% CI)**	**P trend**
Hodgkin lymphoma	15	1.0 (referent)	5	2.18 (0.77-6.19)	7	3.38 (1.30-8.81)	0.01
Myeloid leukemia	27	1.0 (referent)	11	2.09 (1.03–4.26)	10	1.80 (0.85–3.79)	0.06
AML	**21**	**1.0 (referent)**	**7**	**1.71 (0.72–4.07)**	**6**	**1.43 (0.56–3.63)**	**0.31**
CML	**6**	**1.0 (referent)**	**3**	**2.62 (0.64–10.66)**	**4**	**3.07 (0.83–11.40)**	**0.07**

Of 13 AML deaths with peak >2.0 ppm, only 4 had any peak within the 20 years of death; **only 1 AML death occurred (similar to expected) within 2 to** 15 years (typical latency window).

Uncertain relevance of exposure measure – predicted peak exposure – with no measures of actual exposures

No increased risk of AML is seen in relation to occupational exposure to formaldehyde



More complete analysis of Zhang et al. 2010 data

- Zhang et al. (2010) reported significant "changes"* in blood parameters and aneuploidy in in vitro cell cultures.

- Concluded, "formaldehyde exposure can have an adverse effect on the hematopoietic system and that ***leukemia induction by formaldehyde is biologically plausible***, which heightens concerns about its leukemogenic potential from occupational and environmental exposures."

*Study was cross-sectional and reported differences in blood parameters between exposed and unexposed workers were maeasured at one point in time: no changes were investigated over times (boldface emphasis added).

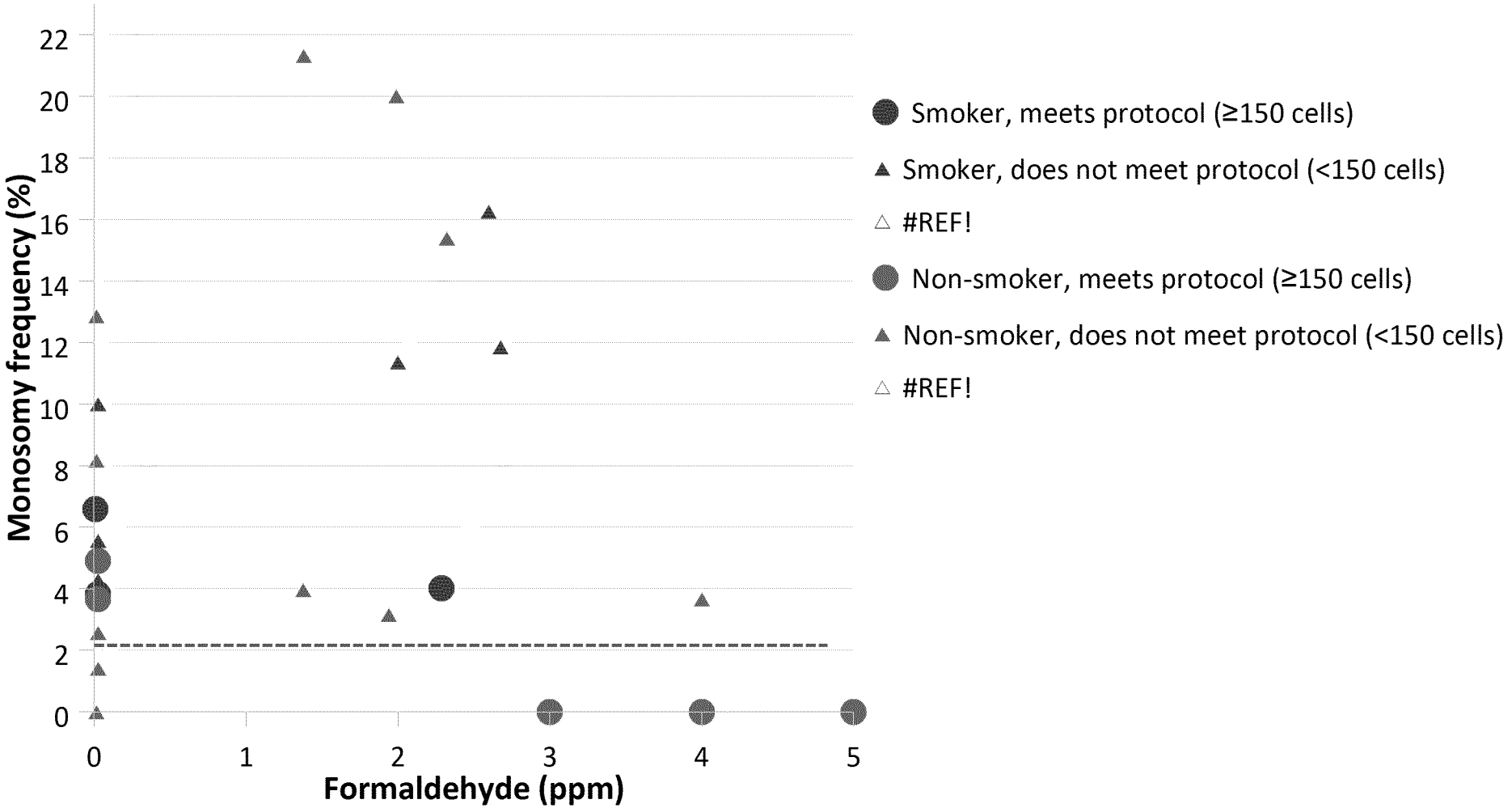
Association between formaldehyde exposure and WBC and RBC counts and components do not show expected dose-response

Exposure	Blood Count Adjusted RR	95% CI	†p-value	Blood Count Adjusted RR	95% CI	†p-value
	WBC			**RBC**		
Unexposed	1.00			1.00		
<1.3 ppm	***0.87**	0.78-0.97		***0.94**	0.91-0.98	
≥1.3 ppm	***0.85**	0.76-0.96	0.943	***0.94**	0.90-0.98	0.947
	Lymphocytes			**Hemoglobin**		
Unexposed	1.00			1.00		
<1.3 ppm	***0.85**	0.75-0.96		0.98	0.94-1.01	
≥1.3 ppm	***0.79**	0.69-0.90	0.660	0.99	0.95-1.03	0.818
	Monocytes			**MCV**		
Unexposed	1.00			1.00		
<1.3 ppm	0.90	0.77-1.06		1.03	0.99-1.08	
≥1.3 ppm	0.89	0.75-1.04	0.973	1.06	1.02-1.11	0.550
	Granulocytes			**Platelets**		
Unexposed	1.00			1.00		
<1.3 ppm	0.87	0.75-1.01		***0.85**	0.75-0.96	
≥1.3 ppm	0.88	0.75-1.03	0.997	0.91	0.80-1.03	0.674

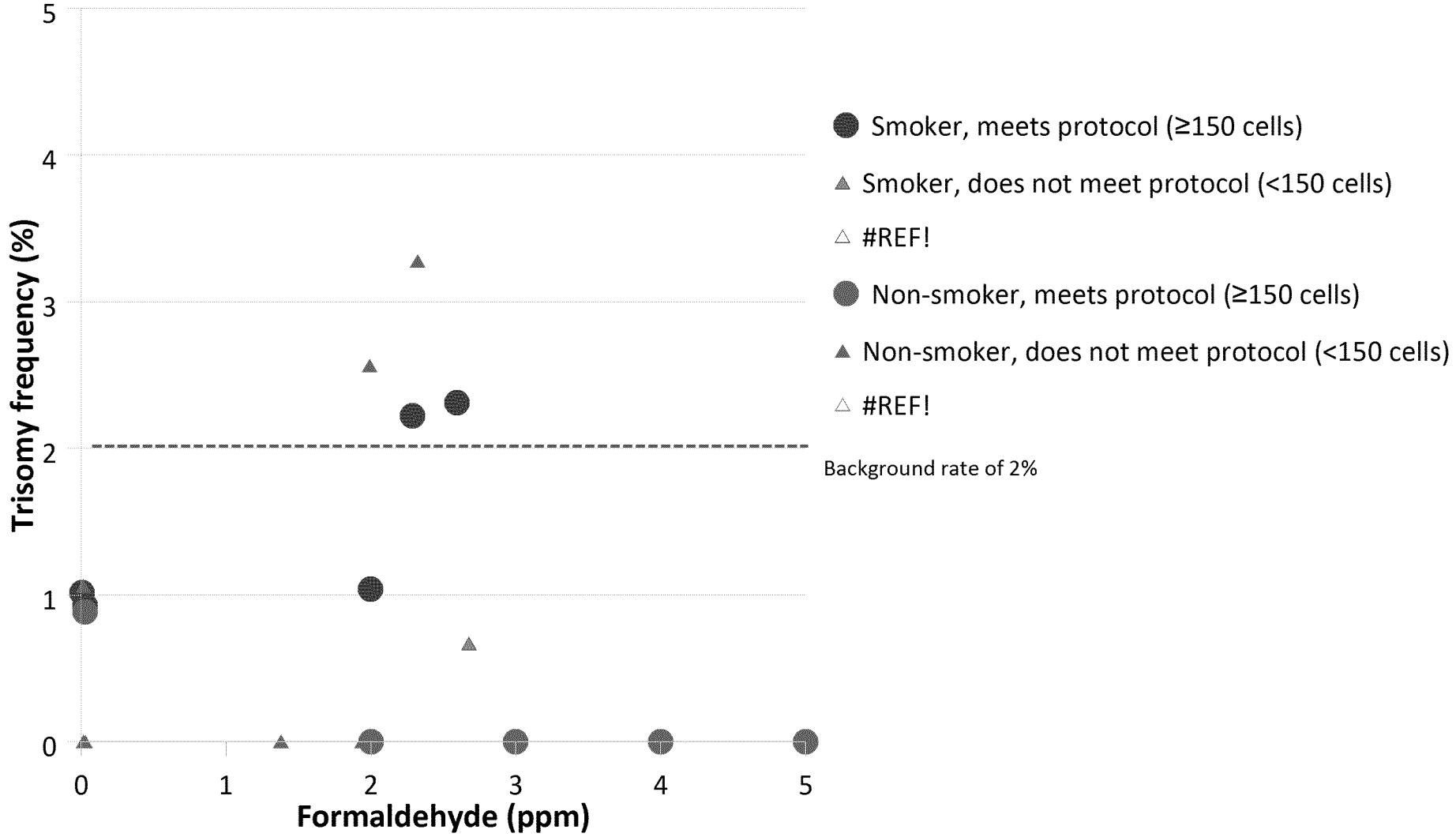
†Comparison between exposed categories

*p<0.05 compared with unexposed

Monosomy 7 – only colored circles met their own internal study protocol



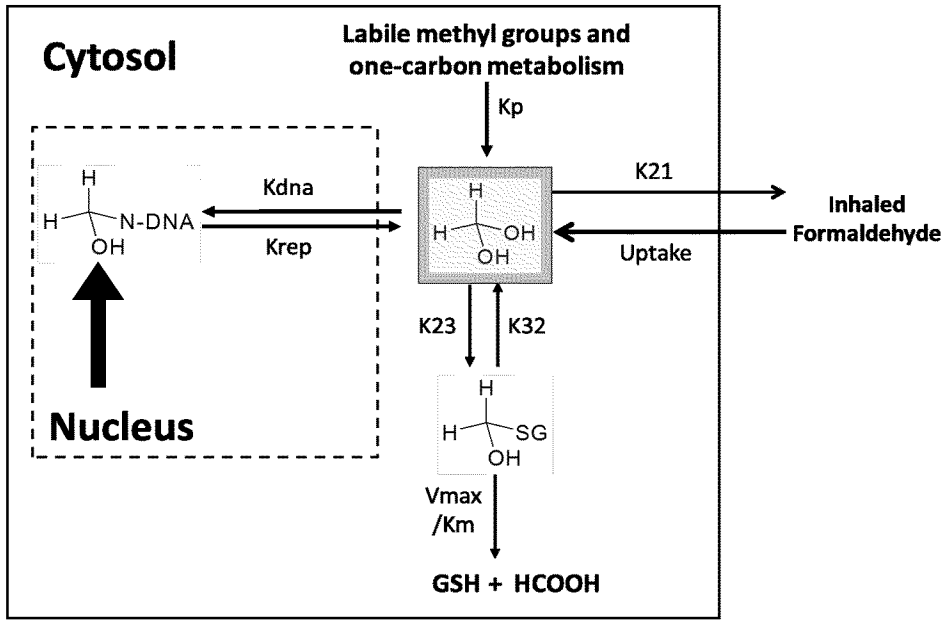
Trisomy 8 - only colored circles met their own internal study protocol



Epidemiological Conclusions

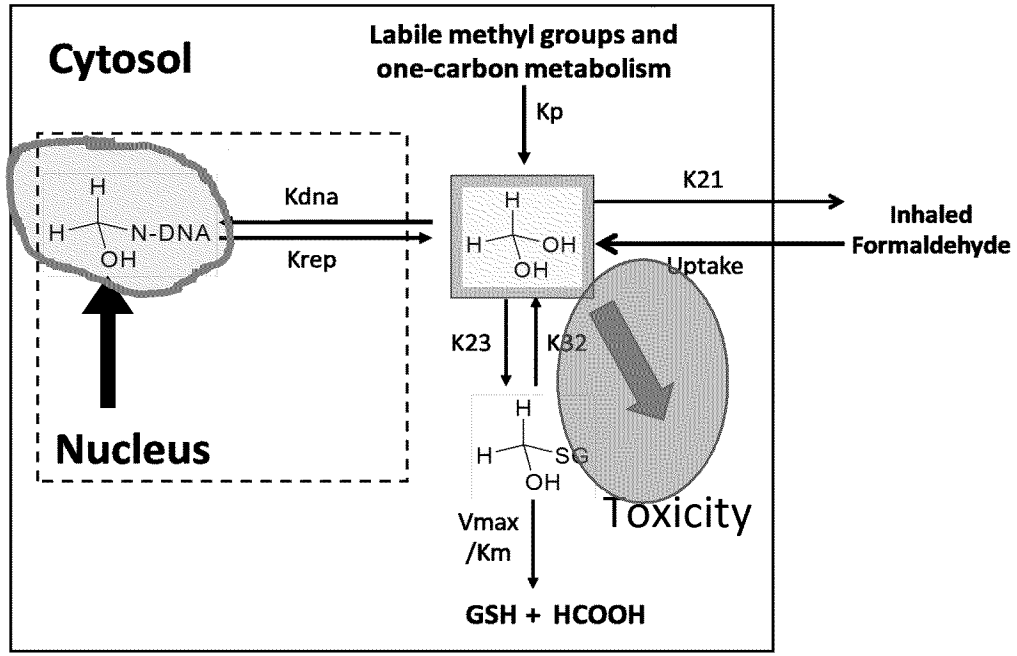
- Epidemiological evaluation of the one cluster of NPC deaths not clearly associated with formaldehyde exposure. Nasal/sino-nasal cancers seemed plausible based on animal studies but increased risk of these tumors has not been seen in the epidemiological studies.
- Conclusions relied upon from Beane Freeman et al. 2010, i.e., association between ML and 'peak' exposure were not verified upon more complete analysis:
  - No excess of ML or AML observed; and
  - Very few decedents with AML had any peak exposure (only 1 within usual latency period).
- Conclusions relied upon from Zhang et al. 2010 inconsistent with fuller analysis of study data, including unreported individual exposure measurements: no associations with exposure level seen among exposed.
- **Weight of evidence synthesis of epidemiological evidence provides vert little support for a causal association between formaldehyde and either NPC or AML.**

III. Integrating studies into a more quantitative risk evaluation



Background: Formaldehyde flux, primarily from tissue to air, with significant background levels of various formaldehyde reaction products

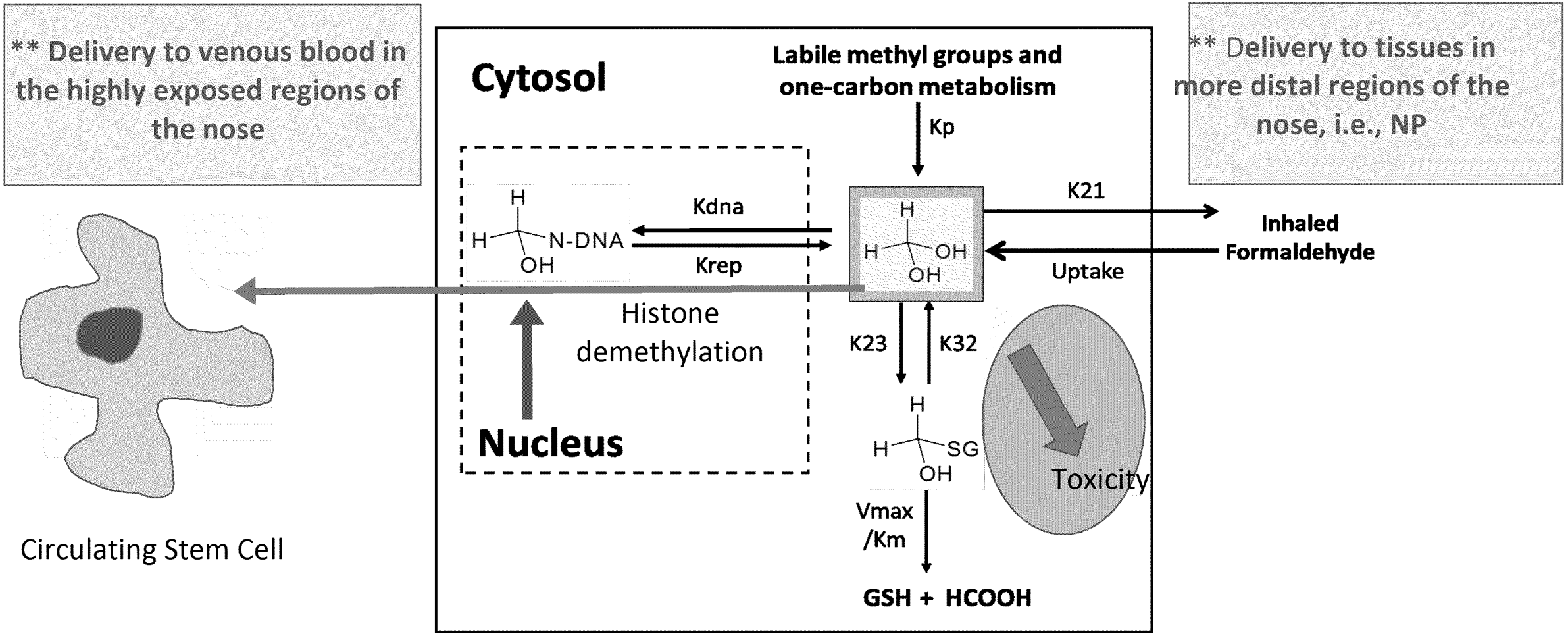
Exposed: Formaldehyde flux, primarily from air to tissue, increases tissue concentration leading to cytotoxicity and increased level of DNA-reaction products



Recommendations/Conclusions: Mode of Action

- The risk assessment for formaldehyde should be structured around a MOA framework based on the extensive understanding of cancer causation in the rat nose
- Measures of DNA-reaction products from formaldehyde should be central considerations in evaluating the ability of inhaled formaldehyde to reach other tissues
- The BBDR model for formaldehyde by Conolly and others could be updated to assist in answering questions about the relative roles of cytotoxicity and DNA-reactivity in cancer in the rat

What would be the proposed MOA for human cancer in light of central role of high doses and cytotoxicity?



** Dosimetry studies indicate that it unlikely that high tissue concentrations can be achieved in any of these more remote tissues.

Recommendations/Conclusions: NP Cancer Epidemiology

- The association of NPC with formaldehyde exposure needs to be examined in light of the animal MOA where tumor formation requires high concentrations of formaldehyde and the presence of relatively high concentrations in all cells.

- Review experience with other human nasal carcinogens to determine whether there are reasons to expect differential sensitivity in particular portions of the human nose compared to the rat.

Recommendations/Conclusions: LHP Cancer Epidemiology

- The association of LHP cancer also needs to be examined in light of the animal MOA where tumor formation requires high concentrations of formaldehyde adding to an already substantial level of cellular formaldehyde.

- Evaluate experience with other other compounds producing leukemia, such as benzene and chemotherapeutic compounds, where bone marrow toxicity is also evident.

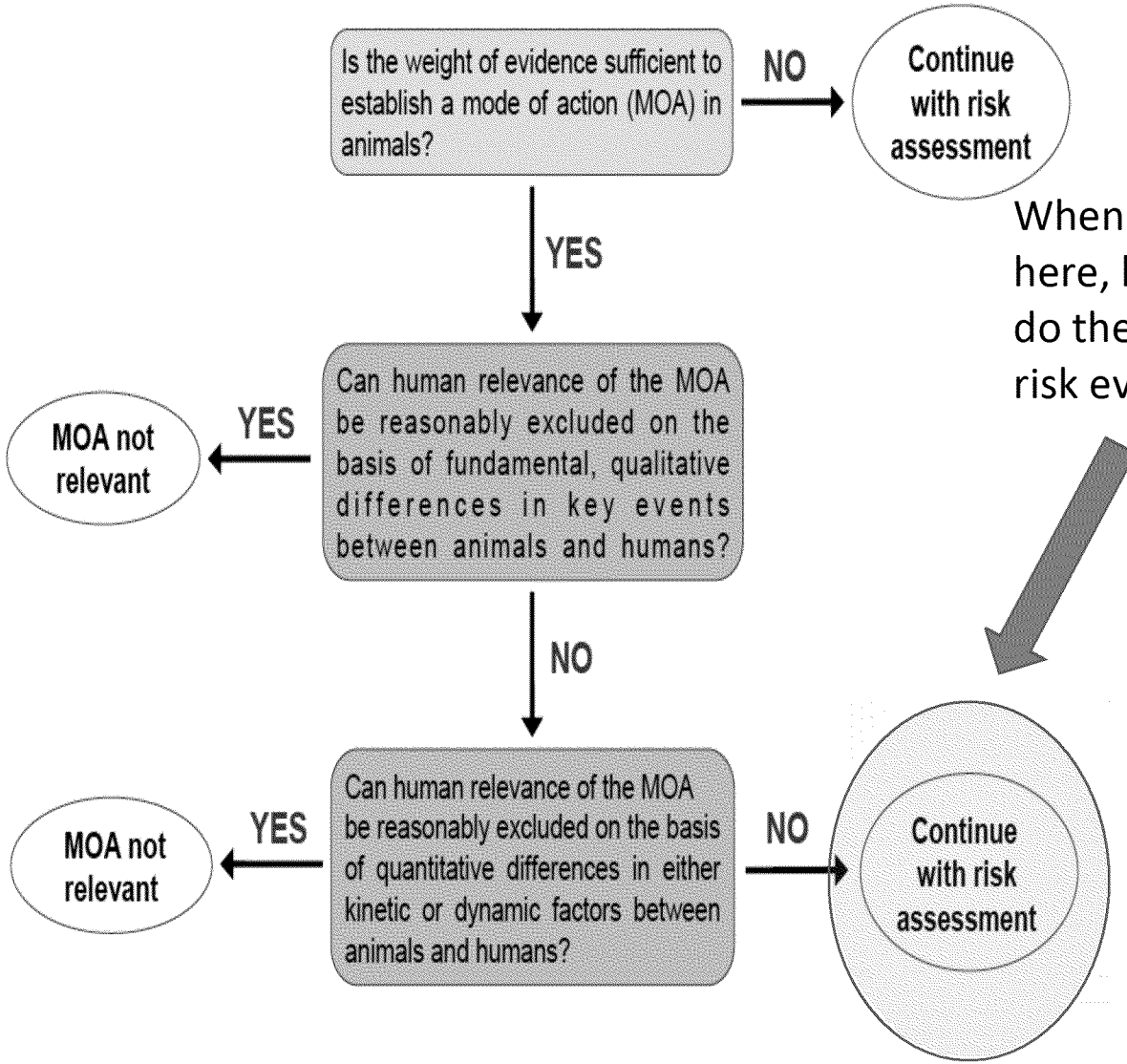
Systematic review is more than just assessing modes-of-action

THE IPCS CONCEPTUAL MOA FRAMEWORK FOR EVALUATING ANIMAL CARCINOGENESIS:

Introduction to the Framework Analysis

- Postulated mode of action (theory of the case)
- Key events
- Concordance of dose-response relationships
- Temporal association
- Strength, consistency and specificity of association of tumour response with key events
- Biological plausibility and coherence
- Other modes of action
- Uncertainties, Inconsistencies, and Data Gaps
- Assessment of postulated mode of action

IPCS general scheme illustrating the main steps in evaluating the human relevance of an animal MOA for tumour formation.



When we end up here, how do we do the quantitative risk evaluation?

Recommendations/Conclusions: The Integrated Risk Evaluation:

- The risk assessment should take into account the weight of evidence for causation of a response by formaldehyde, the concentrations in air and tissues associated with these effects, and the overall evidence for particular modes of action.

- Systematic review needs to evaluate both the qualitative evidence for various MOAs and the manner in which the studies are brought together to support extrapolation models – threshold or low-dose linear - in the quantitative risk assessment.

- This type of robust evaluation appears beyond the scope of present systematic reviews that focus on toxicity rather than the support for extrapolation models based on mode of action studies.

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